

12-14-99

301 Rec'd PCT/PTO 28 DEC 1999

FORM PTO-1390  
(REV. 11-98)U.S. DEPARTMENT OF COMMERCE  
PATENT AND TRADEMARK OFFICE

ATTORNEY'S DOCKET NUMBER

20002YP

**TRANSMITTAL LETTER TO THE UNITED STATES  
DESIGNATED/ELECTED OFFICE (DO/EO/US)  
CONCERNING A FILING UNDER 35 U.S.C. 371**

U.S. APPLICATION NO. (If known, see 37 CFR 1.5)

09/445837

INTERNATIONAL APPLICATION NO.  
PCT/US98/14746INTERNATIONAL FILING DATE  
July 17, 1998PRIORITY DATE CLAIMED  
July 22, 1997

TITLE OF INVENTION

METHOD OF INHIBITING BONE RESORPTION

APPLICANT(S) FOR DO/EO/US

ANASTASIA G. DAIFOTIS, ARTHUR C. SANTORA II, and A. JOHN YATES

**Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:**

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☐ This is an express request to begin national examination procedures [35 U.S.C. 371(f)] at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed [35 U.S.C. 371(c)(2)].
  - a. ☒ is transmitted herewith (required only if not transmitted by the International Bureau).
  - b. ☐ has been transmitted by the International Bureau.
  - c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ A translation of the International Application into English [35 U.S.C. 371(c)(2)].
7. ☒ Amendments to the claims of the International Application under PCT Article 19 [35 U.S.C. 371(c)(3)].
  - a. ☒ are transmitted herewith (required only if not transmitted by the International Bureau). \* Pls see Item 16.
  - b. ☒ have been transmitted by the International Bureau.
  - c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
  - d. ☐ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 [35 U.S.C. 371(c)(3)].
9. ☒ An oath or declaration of the inventor(s) [35 U.S.C. 371(c)(4)].
10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 [35 U.S.C. 371(c)(5)].

**Items 11 to 16 below concern other document(s) or information included:**

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☒ A **FIRST** preliminary amendment.  
☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ☒ Other items or information:

\* NOTE: Amendment of 9 November 1999 is enclosed.


**EXPRESS MAIL CERTIFICATE**

DATE OF DEPOSIT December 13, 1999

EXPRESS MAIL NO. PM358365073US

I HEREBY CERTIFY THAT THIS CORRESPONDENCE IS  
BEING DEPOSITED WITH THE UNITED STATES POSTAL  
SERVICE AS EXPRESS MAIL, "POST OFFICE TO  
ADDRESSEE" BEFORE 5 P.M. ON THE ABOVE DATE IN  
AN ENVELOPE ADDRESSED TO ASSISTANT COMMISSIONER  
FOR PATENTS, WASHINGTON, D.C. 20514.

MAILED BY *[Signature]*  
DATE December 13, 1999

U.S. APPLICATION NO. (if known, see 37 CFR 1.5)		INTERNATIONAL APPLICATION NO.		ATTORNEY'S DOCKET NUMBER	
09/445837		PCT/US98/14746		20002YP	
17. <input checked="" type="checkbox"/> The following fees are submitted: <u>BASIC NATIONAL FEE</u> [37 CFR 1.492(a)(1)-(5)]: Neither international preliminary examination fee (37 CFR 1.482) nor international search fee [37 CFR 1.445(a)(2)] paid to USPTO and International Search Report not prepared by the EPO or JPO..... \$970.00 International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO..... \$840.00 International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee [37 CFR 1.445(a)(2)] paid to USPTO..... \$760.00 International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4)..... \$670.00 International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4)..... \$96.00 <b>ENTER APPROPRIATE BASIC FEE AMOUNT</b> = \$840.00				CALCULATIONS	PTO USE ONLY
Surcharge of <b>\$130.00</b> for furnishing the oath or declaration later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date [37 CFR 1.492(e)].				\$0.00	
Claims	Number Filed	Number Extra	Rate		
Total Claims	1 - 20 =	0	X \$18.00	\$0.00	
Independent Claims	1 - 3 =	0	X \$78.00	\$0.00	
Multiple dependent claim(s) (if applicable)			+ \$260.00	\$0.00	
<b>TOTAL OF ABOVE CALCULATIONS</b>				=	\$840.00
Reduction by 1/2 for filing by small entity, if applicable. Verified Small Entity Statement must also be filed. (Note 37 CFR 1.9, 1.27, 1.28).					
<b>SUBTOTAL</b>				=	\$840.00
Processing fee of <b>\$130.00</b> for furnishing the English translation later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date [37 CFR 1.492(f)].				+	\$0.00
<b>TOTAL NATIONAL FEE</b>				=	\$840.00
Fee for recording the enclosed assignment [37 CFR 1.21(h)]. The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). <b>\$40.00</b> per property.				+	
<b>TOTAL FEES ENCLOSED</b>				=	\$840.00
					Amount to be refunded
					charged
a. <input type="checkbox"/> A check in the amount of \$_____ to cover the above fees is enclosed. b. <input checked="" type="checkbox"/> Please charge my Deposit Account No. <u>13-2755</u> in the amount of <b>\$840.00</b> to cover the above fees. A duplicate copy of this sheet is enclosed. c. <input checked="" type="checkbox"/> The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to the Deposit Account No. <u>13-2755</u> . A duplicate copy of this sheet is enclosed.					
<b>NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive [37 CFR 1.137(a) or (b)] must be filed and granted to restore the application to pending status.</b>					
SEND ALL CORRESPONDENCE TO:					
MERCK & CO., INC. Patent Department, RY60-30 P.O. Box 2000 126 East Lincoln Avenue Rahway, New Jersey 07065-0970			 SIGNATURE		
DATE: <u>December 13, 1999</u>			ANTHONY D. SABATELLI NAME		
PHONE #: <u>(732) 594-1935</u>			34,714 REGISTRATION NUMBER		

09/445837  
514 Rec'd PCT/PTO 13 DEC 1999  
EXPRESS MAIL CERTIFICATE  
DATE OF DEPOSIT December 13, 1999  
EXPRESS MAIL NO. EM358365073US  
I HEREBY CERTIFY THAT THIS CORRESPONDENCE IS  
BEING DEPOSITED WITH THE UNITED STATES POSTAL  
SERVICE AS EXPRESS MAIL "POST OFFICE TO  
ADDRESSEE" BEFORE 5 P.M. ON THE ABOVE DATE IN  
AN ENVELOPE ADDRESSED TO ASSISTANT COMMISSIONER  
FOR PATENTS, WASHINGTON, D.C. 20231.  
MAILED BY [Signature]  
DATE December 13, 1999

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	A.G. Daifotis et al.		Art Unit: 1614
Serial No.:	To Be Assigned	Case No.: 20002YP	
Filed:	December 13, 1999		Examiner: T. Criares
For:	METHOD FOR INHIBITING BONE RESORPTION		

Assistant Commissioner for Patents  
BOX PCT  
Washington, D.C. 20231

PRELIMINARY AMENDMENT

Sir:

Entry of the following Preliminary Amendment is respectfully requested.

IN THE SPECIFICATION:

At p. 1, delete the paragraph below the section labelled "CROSS REFERENCE TO RELATED APPLICATIONS", and substitute therefor the following text:  
-- The present application is the national phase application under 35 U.S.C. §371 of application Serial No. PCT/US98/14796, filed July 17, 1998, which claims priority to U.S. Provisional Application Serial No. 60/053,535, filed July 23, 1997 and U.S. Provisional Application Serial No. 60/053,351, filed July 22, 1997, the contents of all of the foregoing of which are hereby incorporated by reference in their entirety. --

At page 2, line 13, please delete "zolendronate" and replace with -- zoledronate --.

At page 19, line 6, please delete "zolendronate" and replace with -- zoledronate --.

At page 19, line 10, please delete "zolendronate" and replace with -- zoledronate --.

At page 22, line 14, please delete "omprazole" and replace with --omeprazole --.

At page 33, line 33, please delete "zolendronate" and replace with -- zoledronate --.

At page 35, line 1, please delete "zolendronate" and replace with -- zoledronate --.

Insert the Abstract of the Invention as the last page, page 41, of the specification:

-- ABSTRACT OF THE INVENTION

Disclosed are methods for inhibiting bone resorption in mammals while minimizing the occurrence of or potential for adverse gastrointestinal effects. Also disclosed are pharmaceutical compositions and kits for carrying out the therapeutic methods disclosed herein. The compounds are bisphosphonates selected from the group consisting of alendronate, cimidronate, clodronate, tiludronate, [etridronate]etidronate, ibandronate, risedronate, piridronate, pamidronate, [zolendronate]zoledronate, optionally in combination with a histamine H2 antagonist. --

IN THE CLAIMS:

Please cancel Claims 1-52 without prejudice.

Please add the following new Claim 53.

-- 53. A pharmaceutical composition comprising about 140 mg, on an alendronic acid active basis, of a bisphosphonate selected from the group consisting of alendronate, pharmaceutically acceptable salts thereof, and mixtures thereof. --

REMARKS

Claims 1-52 have been cancelled without prejudice, and upon entry of this amendment, Claim 53 will be pending.

No new matter is being added to the above-captioned application by the submission of the Abstract of the Invention, nor by the correction of minor typographical errors in the spelling thereof, because it is substantially identical to that in the priority document PCT/US98/14796. Furthermore, new Claim 53 is *identical* to original Claim 31.

For the Examiner's convenience, a separate sheet for the now *amended* Abstract of the Invention (page 41) is enclosed for inclusion with the specification of the U.S. National Phase Application being filed.

In summary, Applicants respectfully request examination and passage to issue of the present claim.

Respectfully submitted,

Bv

Anthony D. Sabatelli, Reg. No. 34,714  
Attorney for Applicants

/agb  
Enclosure

MERCK & CO., Inc.  
P.O. Box 2000  
Rahway, New Jersey 07065-0907  
Tel: (732) 594-1935

December 13, 1999

TITLE OF THE INVENTION  
METHOD FOR INHIBITING BONE RESORPTION

ABSTRACT OF THE INVENTION

- 5 Disclosed are methods for inhibiting bone resorption in mammals while minimizing the occurrence of or potential for adverse gastrointestinal effects. Also disclosed are pharmaceutical compositions and kits for carrying out the therapeutic methods disclosed herein. The compounds are bisphosphonates selected from the group consisting of alendronate,
- 10 cimidronate, clodronate, tiludronate, etidronate, ibandronate, risedronate, piridronate, pamidronate, zoledronate, optionally in combination with a histamine H2 antagonist.

TITLE OF THE INVENTION  
METHOD FOR INHIBITING BONE RESORPTION

CROSS-REFERENCE TO RELATED APPLICATIONS

- 5           The present invention is related to U.S. application Serial No. 09/060,419, filed April 15, 1998, and U.S. provisional applications Serial Nos. 60/053,535, filed July 23, 1997, and 60/053,351, filed July 22, 1997, the contents of which are hereby incorporated by reference.

10   FIELD OF THE INVENTION

- The present invention relates to oral methods for inhibiting bone resorption in a mammal while minimizing the occurrence of or potential for adverse gastrointestinal effects. These methods comprise orally administering to a mammal in need thereof of a pharmaceutically effective amount of a bisphosphonate as a unit dosage according to a continuous schedule having a dosing interval selected from the group consisting of once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing. The present invention also relates to pharmaceutical compositions and kits useful for carrying out these methods.
- 15  
20

BACKGROUND OF THE INVENTION

- A variety of disorders in humans and other mammals involve or are associated with abnormal bone resorption. Such disorders include, but are not limited to, osteoporosis, Paget's disease, periprosthetic bone loss or osteolysis, and hypercalcemia of malignancy. The most common of these disorders is osteoporosis, which in its most frequent manifestation occurs in postmenopausal women. Osteoporosis is a systemic skeletal disease characterized by a low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture. Because osteoporosis, as well as other disorders associated with bone loss, are chronic conditions, it is believed that appropriate therapy will generally require chronic treatment.
- 25  
30

Multinucleated cells called osteoclasts are responsible for causing bone loss through a process known as bone resorption. It is well known that bisphosphonates are selective inhibitors of osteoclastic bone resorption, making these compounds important therapeutic agents in the treatment or prevention of a variety of generalized or localized bone disorders caused by or associated with abnormal bone resorption. See H. Fleisch, *Bisphosphonates In Bone Disease, From The Laboratory To The Patient*, 2nd Edition, Parthenon Publishing (1995), which is incorporated by reference herein in its entirety.

At present, a great amount of preclinical and clinical data exists for the potent bisphosphonate compound alendronate. Evidence suggests that other bisphosphonates such as risedronate, tiludronate, ibandronate and zoledronate, have many properties in common with alendronate, including high potency as inhibitors of osteoclastic bone resorption. An older bisphosphonate compound, etidronate, also inhibits bone resorption. However, unlike the more potent bisphosphonates, etidronate impairs mineralization at doses used clinically, and may give rise to osteomalacia, a condition resulting in an undesirable decrease in bone mineralization. See Boyce, B. F., Fogelman, I., Ralston, S. et al. (1984) *Lancet* 1(8381), pp. 821-824 (1984), and Gibbs, C. J., Aaron, J. E.; Peacock, M. (1986) *Br. Med. J.* 292, pp. 1227-1229 (1986), both of which are incorporated by reference herein in their entirety.

Despite their therapeutic benefits, bisphosphonates are poorly absorbed from the gastrointestinal tract. See B.J. Gertz et al., *Clinical Pharmacology of Alendronate Sodium, Osteoporosis Int.*, Suppl. 3: S13-16 (1993) and B.J. Gertz et al., *Studies of the oral bioavailability of alendronate, Clinical Pharmacology & Therapeutics*, vol. 58, number 3, pp. 288-298 (September 1995), which are incorporated by reference herein in their entirety. Intravenous administration has been used to overcome this bioavailability problem. However, intravenous administration is costly and inconvenient, especially when the patient must be given an intravenous infusion lasting several hours on repeated occasions.

If oral administration of the bisphosphonate is desired, relatively high doses must be administered to compensate for the low bioavailability from the gastrointestinal tract. To offset this low



bioavailability, it is generally recommended that the patient take the bisphosphonate on an empty stomach and fast for at least 30 minutes afterwards. However, many patients find the need for such fasting on a daily basis to be inconvenient. Moreover, oral administration has been associated with adverse gastrointestinal effects, especially those relating to the esophagus. See Fleisch, Id. These effects appear to be related to the irritant potential of the bisphosphonate in the esophagus, a problem which is exacerbated by the presence of refluxed gastric acid. For example, the bisphosphonate, pamidronate has been associated with esophageal ulcers. See E.G. Lufkin et al., *Pamidronate: An Unrecognized Problem in Gastrointestinal Tolerability, Osteoporosis International*, 4: 320-322 (1994), which is incorporated by reference herein in its entirety. Although not as common, the use of alendronate has been associated with esophagitis and/or esophageal ulcers. See P.C. De Groen, et al., *Esophagitis Associated With The Use Of Alendronate, New England Journal of Medicine*, vol. 335, no. 124, pp. 1016-1021 (1996), D.O. Castell, *Pill Esophagitis -- The Case of Alendronate, New England Journal of Medicine*, vol. 335, no. 124, pp. 1058-1059 (1996), and U.A. Liberman et al., *Esophagitis and Alendronate, New England Journal of Medicine*, vol. 335, no. 124, pp. 1069-1070 (1996), which are incorporated by reference herein in their entirety. The degree of adverse gastrointestinal effects of bisphosphonates has been shown to increase with increasing dose. See C.H. Chestnut et al., *Alendronate Treatment of the Postmenopausal Osteoporotic Woman: Effect of Multiple Dosages on Bone Mass and Bone Remodeling, The American Journal of Medicine*, vol. 99, pp. 144-152, (August 1995), which is incorporated by reference herein in its entirety. Also, these adverse esophageal effects appear to be more prevalent in patients who do not take the bisphosphonate with an adequate amount of liquid or who lie down shortly after dosing, thereby increasing the chance for esophageal reflux.

Current oral bisphosphonate therapies generally fail into two categories: (1) those therapies utilizing continuous daily treatment, and (2) those therapies utilizing a cyclic regimen of treatment and rest periods.

The continuous daily treatment regimens normally involve the chronic administration of relatively low doses of the bisphosphonate compound, with the objective of delivering the desired cumulative therapeutic dose over the course of the treatment period. However, continuous daily dosing has the potential disadvantage of causing adverse gastrointestinal effects due to the repetitive, continuous, and additive irritation to the gastrointestinal tract. Also, because bisphosphonates should be taken on an empty stomach followed by fasting and maintenance of an upright posture for at least 30 minutes, many patients find daily dosing to be burdensome. These factors can therefore interfere with patient compliance, and in severe cases even require cessation of treatment.

Cyclic treatment regimens were developed because some bisphosphonates, such as etidronate, when given daily for more than several days, have the disadvantage of actually causing a decline in bone mineralization, i.e. osteomalacia. U.S. Patent No. 4,761,406, to Flora et al, issued August 2, 1988, which is incorporated by reference herein in its entirety, describes a cyclic regimen developed in an attempt to minimize the decline in bone mineralization while still providing a therapeutic anti-resorptive effect. Generally, cyclic regimens are characterized as being intermittent, as opposed to continuous treatment regimens, and have both treatment periods during which the bisphosphonate is administered and nontreatment periods to permit the systemic level of the bisphosphonate to return to baseline. However, the cyclic regimens, relative to continuous dosing, appear to result in a decreased therapeutic antiresorptive efficacy. Data on risedronate suggests that cyclic dosing is actually less effective than continuous daily dosing for maximizing antiresorptive bone effects. See L. Mortensen, et al., *Prevention Of Early Postmenopausal Bone Loss By Risedronate*, *Journal of Bone and Mineral Research*, vol. 10, supp. 1, p. s140 (1995), which is incorporated by reference herein in its entirety. Furthermore, these cyclic regimens do not eliminate or minimize adverse gastrointestinal effects, because such regimens typically utilize periods of multiple daily dosing. Also, the cyclic regimens are cumbersome to administer and have the disadvantage of low patient

compliance, and consequently compromised therapeutic efficacy. U.S. Patent No. 5,366,965, to Strein, issued November 22, 1994, which is incorporated by reference herein in its entirety, attempts to address the problem of adverse gastrointestinal effects by administering a polyphosphonate compound, either orally, subcutaneously, or intravenously, according to an intermittent dosing schedule having both a bone resorption inhibition period and a no-treatment rest period. However, the regimen has the disadvantage of not being continuous and regular, and requires nontreatment periods ranging from 20 to 120 days. PCT Application No. WO 95/30421, to Goodship et al, published November 16, 1995, which is incorporated by reference herein in its entirety, discloses methods for preventing prosthetic loosening and migration using various bisphosphonate compounds. Administration of a once weekly partial dose of the bisphosphonate is disclosed. However, the reference specifically fails to address the issue of adverse gastrointestinal effects or to disclose administration of larger or multiple dosages.

It is seen from current teachings that both daily and cyclic treatment regimens have shortcomings, and that there is a need for development of a dosing regimen to overcome these shortcomings.

In the present invention, it is found that the adverse gastrointestinal effects that can be associated with daily or cyclic dosing regimens can be minimized by administering the bisphosphonate at a relatively high unit dosage according to a continuous schedule having a dosing interval selected from the group consisting of once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing. In other words, it is found that the administration of a bisphosphonate at a high relative dosage at a low relative dosing frequency causes less adverse gastrointestinal effects, particularly esophageal effects, compared to the administration of a low relative dosage at a high relative dosing frequency. This result is surprising in view of the teachings suggesting that adverse gastrointestinal effects would be expected to increase as a function of increasing bisphosphonate dosage. Such administration methods of the present invention would be especially beneficial in treating patients that have been identified as suffering from

or are susceptible to upper gastrointestinal disorders, e.g. gastrointestinal reflux disease (i.e. "GERD"), esophagitis, dyspepsia (i.e. heartburn), ulcers, and other related disorders. In such patients conventional bisphosphonate therapy could potentially exacerbate or induce such upper gastrointestinal disorders.

From a patient lifestyle standpoint, the methods of the present invention would also be more convenient than daily or cyclic dosing regimens. Patients would be subjected less frequently to the inconvenience of having to take the drug on an empty stomach and having to fast for at least 30 minutes after dosing. Also, patients would not need to keep track of a complex dosing regimen. The methods of the present invention are likely to have the advantage of promoting better patient compliance, which in turn can translate into better therapeutic efficacy.

It is an object of the present invention to provide methods for inhibiting bone resorption and the conditions associated therewith.

It is another object of the present invention to provide methods for treating abnormal bone resorption and the conditions associated therewith

It is another object of the present invention to provide methods for preventing abnormal bone resorption and the conditions associated therewith.

It is another object of the present invention to provide methods which are oral methods.

It is another object of the present invention to provide such methods in humans.

It is another object of the present invention to provide such methods in patients that have been identified as suffering from or are susceptible to upper gastrointestinal disorders, e.g. gastrointestinal reflux disease (i.e. "GERD"), esophagitis, dyspepsia (i.e. heartburn), ulcers, and other related disorders.

It is another object of the present invention to provide such methods while minimizing the occurrence of or potential for adverse gastrointestinal effects.

It is another object of the present invention to provide such methods comprising a continuous dosing schedule having a dosing interval selected from the group consisting of weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing.

- 5 It is another object of the present invention to provide such methods comprising a continuous dosing schedule having a dosing periodicity ranging from about once every 3 days to about once every 16 days.

- 10 It is another object of the present invention to provide such methods wherein the continuous dosing schedule is maintained until the desired therapeutic effect is achieved.

It is another object of the present invention to treat or prevent abnormal bone resorption in an osteoporotic mammal, preferably an osteoporotic human.

- 15 It is another object of the present invention to provide pharmaceutical compositions and kits useful in the methods herein.

These and other objects will become readily apparent from the detailed description which follows.

## 20 SUMMARY OF THE INVENTION

- The present invention relates to methods for inhibiting bone resorption in a mammal in need thereof, while minimizing the occurrence of or potential for adverse gastrointestinal effects, said method comprising orally administering to said mammal a
- 25 pharmaceutically effective amount of a bisphosphonate as a unit dosage according to a continuous schedule having a dosing interval selected from the group consisting of once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing, wherein said continuous schedule is maintained until the desired therapeutic effect is achieved
- 30 for said mammal.

In other embodiments, the present invention relates to methods comprising a continuous dosing schedule having a dosing periodicity ranging from about once every 3 days to about once every 16 days.

In other embodiments, the present invention relates to methods for treating abnormal bone resorption in a mammal in need of such treatment.

5 In other embodiments, the present invention relates to methods for preventing abnormal bone resorption in a mammal in need of such prevention.

In other embodiments, the present invention relates to such methods useful in humans.

10 In other embodiments, the present invention relates to such methods useful in humans indentified as having or being susceptible to upper gastrointestinal disorders.

In other embodiments, the present invention relates to methods for treating or preventing osteoporosis in a mammal.

15 In other embodiments, the present invention relates to methods for treating or preventing osteoporosis in a human.

In other embodiments, the present invention relates to methods for inhibiting bone resorption, or treating or preventing abnormal bone resorption in a human comprising administering to said human from about 8.75 mg to about 140 mg, on an alendronic acid active  
20 basis, of a bisphosphonate selected from the group consisting of alendronate, pharmaceutically acceptable salts thereof, and mixtures thereof.

In other embodiments the present invention relates to a pharmaceutical composition comprising from about 8.75 mg to about 140  
25 mg, on an alendronic acid active basis, of a bisphosphonate selected from the group consisting of alendronate, pharmaceutically acceptable salts thereof, and mixtures thereof.

All percentages and ratios used herein, unless otherwise indicated, are by weight. The invention hereof can comprise, consist of,  
30 or consist essentially of the essential as well as optional ingredients, components, and methods described herein.

#### BRIEF DESCRIPTION OF THE FIGURES

FIG. 1 is a photomicrograph (total magnification 270X) of canine  
35 esophagus tissue (paraffin embedded and stained with hematoxylin and

eosin) from an animal sacrificed immediately after infusion of the last of five separate dosages of 50 mL of simulated gastric juice administered on five consecutive days.

FIG. 2 is a photomicrograph (total magnification 270X) of canine esophagus tissue (paraffin embedded and stained with hematoxylin and eosin) from an animal sacrificed immediately after infusion of the last of five separate dosages of 50 mL of 0.20 mg/mL alendronate in simulated gastric juice administered on five consecutive days.

FIG. 3 is a photomicrograph (total magnification 270X) of canine esophagus tissue (paraffin embedded and stained with hematoxylin and eosin) from an animal sacrificed 24 hours after infusion with a single dosage of 50 mL of 0.80 mg/mL alendronate in simulated gastric juice.

FIG. 4 is a photomicrograph (total magnification 270X) of canine esophagus tissue (paraffin embedded and stained with hematoxylin and eosin) from an animal sacrificed 7 days after infusion with a single dosage of 50 mL of 0.80 mg/mL alendronate in simulated gastric juice.

FIG. 5 is a photomicrograph (total magnification 270X) of canine esophagus tissue (paraffin embedded and stained with hematoxylin and eosin) from an animal sacrificed 7 days after infusion of the last of 4 separate dosages of 50 mL of 0.80 mg/mL alendronate in simulated gastric juice administered once per week, i.e. once every 7 days.

FIG. 6 is a photomicrograph (total magnification 270X) of canine esophagus tissue (paraffin embedded and stained with hematoxylin and eosin) from an animal sacrificed 4 days after infusion of the last of 8 separate dosages of 50 mL of 0.40 mg/mL alendronate in simulated gastric juice administered twice per week, i.e. once every 3-4 days.

FIG. 7 is a photomicrograph (total magnification 270X) of canine esophagus tissue (paraffin embedded and stained with hematoxylin and eosin) from an animal sacrificed immediately after infusion of the last of five separate dosages of 50 mL of 0.20 mg/mL risedronate in simulated gastric juice administered on five consecutive days.

FIG. 8 is a photomicrograph (total magnification 270X) of canine esophagus tissue (paraffin embedded and stained with hematoxylin and eosin) from an animal sacrificed immediately after infusion of the last of

five separate dosages of 50 mL of 4.0 mg/mL tiludronate in simulated gastric juice administered on five consecutive days.

#### DESCRIPTION OF THE INVENTION

5           The present invention relates to a method, preferably an oral method, for inhibiting bone resorption in a mammal in need thereof, while minimizing the occurrence of or potential for adverse gastrointestinal effects. The present invention relates to methods of  
10   treating or preventing abnormal bone resorption in a mammal in need of such treatment or prevention. The methods of the present invention comprise orally administering to a mammal a pharmaceutically effective amount of a bisphosphonate as a unit dosage, wherein said dosage is administered according to a continuous schedule having a dosing interval selected from the group consisting of once-weekly dosing,  
15   twice-weekly dosing, biweekly dosing, and twice-monthly dosing. In other embodiments, the present invention relates to methods comprising a continuous dosing schedule having a dosing periodicity ranging from about once every 3 days to about once every 16 days. Typically, the continuous dosing schedule is maintained until the desired therapeutic  
20   effect is achieved for the mammal.

          The present invention utilizes higher unit dosages of the bisphosphonate at each dosing point than has heretofore been typically administered, yet because of the dosing schedule chosen, the potential for adverse gastrointestinal effects are minimized. Moreover, the  
25   method is more convenient because the disadvantages associated with daily dosing are minimized.

          The methods of the present invention are generally administered to mammals in need of bisphosphonate therapy. Preferably the mammals are human patients, particularly human  
30   patients in need of inhibiting bone resorption, such as patients in need of treating or preventing abnormal bone resorption.

          The administration methods of the present invention are especially useful in administering bisphosphonate therapy to human patients that have been identified as suffering from or are susceptible to  
35   upper gastrointestinal disorders, e.g. GERD, esophagitis, dyspepsia,



ulcers, etc. In such patients conventional bisphosphonate therapy could potentially exacerbate or induce such upper gastrointestinal disorders.

The term "pharmaceutically effective amount", as used herein, means that amount of the bisphosphonate compound, that will elicit the desired therapeutic effect or response when administered in accordance with the desired treatment regimen. A preferred pharmaceutically effective amount of the bisphosphonate is a bone resorption inhibiting amount.

The term "minimize the occurrence of or potential for adverse gastrointestinal effects", as used herein, means reducing, preventing, decreasing, or lessening the occurrence of or the potential for incurring unwanted side effects in the gastrointestinal tract, i.e. the esophagus, stomach, intestines, and rectum, particularly the upper gastrointestinal tract, i.e. the esophagus and stomach. Nonlimiting adverse gastrointestinal effects include, but are not limited to GERD, esophagitis, dyspepsia, ulcers, esophageal irritation, esophageal perforation, abdominal pain, and constipation.

The term "abnormal bone resorption", as used herein means a degree of bone resorption that exceeds the degree of bone formation, either locally, or in the skeleton as a whole. Alternatively, "abnormal bone resorption" can be associated with the formation of bone having an abnormal structure.

The term "bone resorption inhibiting", as used herein, means treating or preventing bone resorption by the direct or indirect alteration of osteoclast formation or activity. Inhibition of bone resorption refers to treatment or prevention of bone loss, especially the inhibition of removal of existing bone either from the mineral phase and/or the organic matrix phase, through direct or indirect alteration of osteoclast formation or activity.

The terms "continuous schedule" or "continuous dosing schedule", as used herein, mean that the dosing regimen is repeated until the desired therapeutic effect is achieved. The continuous schedule or continuous dosing schedule is distinguished from cyclical or intermittent administration.

5 The term "until the desired therapeutic effect is achieved",  
as used herein, means that the bisphosphonate compound is  
continuously administered, according to the dosing schedule chosen, up  
to the time that the clinical or medical effect sought for the disease or  
condition is observed by the clinician or researcher. For methods of  
treatment of the present invention, the bisphosphonate compound is  
continuously administered until the desired change in bone mass or  
structure is observed. In such instances, achieving an increase in bone  
mass or a replacement of abnormal bone structure with more normal  
bone structure are the desired objectives. For methods of prevention of  
10 the present invention, the bisphosphonate compound is continuously  
administered for as long as necessary to prevent the undesired  
condition. In such instances, maintenance of bone mass density is often  
the objective. Nonlimiting examples of administration periods can  
15 range from about 2 weeks to the remaining lifespan of the mammal. For  
humans, administration periods can range from about 2 weeks to the  
remaining lifespan of the human, preferably from about 2 weeks to about  
20 years, more preferably from about 1 month to about 20 years, more  
preferably from about 6 months to about 10 years, and most preferably  
20 from about 1 year to about 10 years.

#### Methods of the Present Invention

The present invention comprises methods for inhibiting  
bone resorption in mammals. The present invention also comprises  
25 treating abnormal bone resorption in mammals. The present invention  
also comprises methods for preventing abnormal bone resorption in  
mammals. In preferred embodiments of the present invention, the  
mammal is a human.

The methods of the present invention do not have the  
30 disadvantages of current methods of treatment which can cause or  
increase the potential for adverse gastrointestinal effects or which  
require cumbersome, irregular, or complicated dosing regimens.

The present invention comprises a continuous dosing  
schedule whereby a unit dosage of the bisphosphonate is regularly  
35 administered according to a dosing interval selected from the group

consisting of once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing.

By once-weekly dosing is meant that a unit dosage of the bisphosphonate is administered once a week, i.e. one time during a seven day period, preferably on the same day of each week. In the once-weekly dosing regimen, the unit dosage is generally administered about every seven days. A nonlimiting example of a once-weekly dosing regimen would entail the administration of a unit dosage of the bisphosphonate every Sunday. It is preferred that the unit dosage is not administered on consecutive days, but the once-weekly dosing regimen can include a dosing regimen in which unit dosages are administered on two consecutive days falling within two different weekly periods.

By twice-weekly dosing is meant that a unit dosage of the bisphosphonate is administered twice a week, i.e. two times during a seven day period, preferably on the same two days of each weekly period. In the twice-weekly dosing regimen, each unit dosage is generally administered about every three to four days. A nonlimiting example of a twice-weekly dosing regimen would entail the administration of a unit dosage of the bisphosphonate every Sunday and Wednesday. It is preferred that the unit dosages are not administered on the same or consecutive days, but the twice-weekly dosing regimen can include a dosing regimen in which unit dosages are administered on two consecutive days within a weekly period or different weekly periods.

By biweekly dosing is meant that a unit dosage of the bisphosphonate is administered once during a two week period, i.e. one time during a fourteen day period, preferably on the same day during each two week period. In the twice-weekly dosing regimen, each unit dosage is generally administered about every fourteen days. A nonlimiting example of a biweekly dosing regimen would entail the administration of a unit dosage of the bisphosphonate every other Sunday. It is preferred that the unit dosage is not administered on consecutive days, but the biweekly dosing regimen can include a dosing regimen in which the unit dosage is administered on two consecutive days within two different biweekly periods.

0445637 121399  
66127 294460

By twice-monthly dosing is meant that a unit dosage of the bisphosphonate is administered twice, i.e. two times, during a monthly calendar period. With the twice-monthly regimen, the doses are preferably given on the same two dates of each month. In the twice-monthly dosing regimen, each unit dosage is generally administered about every fourteen to sixteen days. A nonlimiting example of a biweekly dosing regimen would entail dosing on or about the first of the month and on or about the fifteenth, i.e. the midway point, of the month. It is preferred that the unit dosages are not administered on the same or consecutive days but the twice-monthly dosing regimen can include a dosing regimen in which the unit dosages are administered on two consecutive days within a monthly period, or different monthly periods. The twice-monthly regimen is defined herein as being distinct from, and not encompassing, the biweekly dosing regimen because the two regimens have a different periodicity and result in the administration of different numbers of dosages over long periods of time. For example, over a one year period, a total of about twenty four dosages would be administered according to the twice-monthly regimen (because there are twelve calendar months in a year), whereas a total of about twenty six dosages would be administered according to the biweekly dosing regimen (because there are about fifty-two weeks in a year).

In further embodiments or descriptions of the present invention, the unit dosage is given with a periodicity ranging from about once every 3 days to about once every 16 days.

The methods and compositions of the present invention are useful for inhibiting bone resorption and for treating and preventing abnormal bone resorption and conditions associated therewith. Such conditions include both generalized and localized bone loss. Also, the creation of bone having an abnormal structure, as in Paget's disease, can be associated with abnormal bone resorption. The term "generalized bone loss" means bone loss at multiple skeletal sites or throughout the skeletal system. The term "localized bone loss" means bone loss at one or more specific, defined skeletal sites.

Generalized bone loss is often associated with osteoporosis. Osteoporosis is most common in post-menopausal women, wherein

estrogen production has been greatly diminished. However, osteoporosis can also be steroid-induced and has been observed in males due to age. Osteoporosis can be induced by disease, e.g. rheumatoid arthritis, it can be induced by secondary causes, e.g., glucocorticoid therapy, or it can come about with no identifiable cause, i.e. idiopathic osteoporosis. In the present invention, preferred methods include the treatment or prevention of abnormal bone resorption in osteoporotic humans.

Localized bone loss has been associated with periodontal disease, with bone fractures, and with periprosthetic osteolysis (in other words where bone resorption has occurred in proximity to a prosthetic implant).

Generalized or localized bone loss can occur from disuse, which is often a problem for those confined to a bed or a wheelchair, or for those who have an immobilized limb set in a cast or in traction.

The methods and compositions of the present invention are useful for treating and or preventing the following conditions or disease states: osteoporosis, which can include post-menopausal osteoporosis, steroid-induced osteoporosis, male osteoporosis, disease-induced osteoporosis, idiopathic osteoporosis; Paget's disease; abnormally increased bone turnover; periodontal disease; localized bone loss associated with periprosthetic osteolysis; and bone fractures.

The methods of the present invention are intended to specifically exclude methods for the treatment and/or prevention of prosthesis loosening and prosthesis migration in mammals as described in PCT application WO 95/30421, to Goodship et al, published November 16, 1995, which is incorporated by reference herein in its entirety.

### Bisphosphonates

The methods and compositions of the present invention comprise a bisphosphonate. The bisphosphonates of the present invention correspond to the chemical formula



wherein

- 5 A and X are independently selected from the group consisting of H, OH, halogen, NH<sub>2</sub>, SH, phenyl, C1-C30 alkyl, C1-C30 substituted alkyl, C1-C10 alkyl or dialkyl substituted NH<sub>2</sub>, C1-C10 alkoxy, C1-C10 alkyl or phenyl substituted thio, C1-C10 alkyl substituted phenyl, pyridyl, furanyl, pyrrolidinyl, imidazonyl, and benzyl.

- 10 In the foregoing chemical formula, the alkyl groups can be straight, branched, or cyclic, provided sufficient atoms are selected for the chemical formula. The C1-C30 substituted alkyl can include a wide variety of substituents, nonlimiting examples which include those selected from the group consisting of phenyl, pyridyl, furanyl, pyrrolidinyl, imidazonyl, NH<sub>2</sub>, C1-C10 alkyl or dialkyl substituted NH<sub>2</sub>,  
15 OH, SH, and C1-C10 alkoxy.

In the foregoing chemical formula, A can include X and X can include A such that the two moieties can form part of the same cyclic structure.

- 20 The foregoing chemical formula is also intended to encompass complex carbocyclic, aromatic and hetero atom structures for the A and/or X substituents, nonlimiting examples of which include naphthyl, quinolyl, isoquinolyl, adamantyl, and chlorophenylthio.

- Preferred structures are those in which A is selected from the group consisting of H, OH, and halogen, and X is selected from the  
25 group consisting of C1-C30 alkyl, C1-C30 substituted alkyl, halogen, and C1-C10 alkyl or phenyl substituted thio.

- More preferred structures are those in which A is selected from the group consisting of H, OH, and Cl, and X is selected from the  
30 group consisting of C1-C30 alkyl, C1-C30 substituted alkyl, Cl, and chlorophenylthio.

Most preferred is when A is OH and X is a 3-aminopropyl moiety, so that the resulting compound is a 4-amino-1-hydroxybutylidene-1,1-bisphosphonate, i.e. alendronate.

Pharmaceutically acceptable salts and derivatives of the bisphosphonates are also useful herein. Nonlimiting examples of salts include those selected from the group consisting alkali metal, alkaline metal, ammonium, and mono-, di, tri-, or tetra-C1-C30-alkyl-substituted ammonium. Preferred salts are those selected from the group consisting of sodium, potassium, calcium, magnesium, and ammonium salts. Nonlimiting examples of derivatives include those selected from the group consisting of esters, hydrates, and amides.

"Pharmaceutically acceptable" as used herein means that the salts and derivatives of the bisphosphonates have the same general pharmacological properties as the free acid form from which they are derived and are acceptable from a toxicity viewpoint.

It should be noted that the terms "bisphosphonate" and "bisphosphonates", as used herein in referring to the therapeutic agents of the present invention are meant to also encompass diphosphonates, biphosphonic acids, and diphosphonic acids, as well as salts and derivatives of these materials. The use of a specific nomenclature in referring to the bisphosphonate or bisphosphonates is not meant to limit the scope of the present invention, unless specifically indicated. Because of the mixed nomenclature currently in use by those of ordinary skill in the art, reference to a specific weight or percentage of a bisphosphonate compound in the present invention is on an acid active weight basis, unless indicated otherwise herein. For example, the phrase "about 70 mg of a bone resorption inhibiting bisphosphonate selected from the group consisting of alendronate, pharmaceutically acceptable salts thereof, and mixtures thereof, on an alendronic acid active weight basis" means that the amount of the bisphosphonate compound selected is calculated based on 70 mg of alendronic acid.

Nonlimiting examples of bisphosphonates useful herein include the following:

Alendronic acid, 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid.

Alendronate (also known as alendronate sodium or monosodium trihydrate), 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium trihydrate.

Alendronic acid and alendronate are described in U.S.

- 5 Patents 4,922,007, to Kieczkowski et al., issued May 1, 1990, and 5,019,651, to Kieczkowski, issued May 28, 1991, both of which are incorporated by reference herein in their entirety.

- Cycloheptylaminomethylene-1,1-bisphosphonic acid, YM 175, Yamanouchi (cimadronate), as described in U.S. Patent 10 4,970,335, to Isomura et al., issued November 13, 1990, which is incorporated by reference herein in its entirety.

- 1,1-dichloromethylene-1,1-diphosphonic acid (clodronic acid), and the disodium salt (clodronate, Procter and Gamble), are described in Belgium Patent 672,205 (1966) and *J. Org. Chem* 32, 4111 15 (1967), both of which are incorporated by reference herein in their entirety.

1-hydroxy-3-(1-pyrrolidinyl)-propylidene-1,1-bisphosphonic acid (EB-1053).

- 1-hydroxyethane-1,1-diphosphonic acid (etidronic acid). 20 1-hydroxy-3-(N-methyl-N-pentylamino)propylidene-1,1-bisphosphonic acid, also known as BM-210955, Boehringer-Mannheim (ibandronate), is described in U.S. Patent No. 4,927,814, issued May 22, 1990, which is incorporated by reference herein in its entirety.

- 25 6-amino-1-hydroxyhexylidene-1,1-bisphosphonic acid (neridronate).

3-(dimethylamino)-1-hydroxypropylidene-1,1-bisphosphonic acid (olpadronate).

- 30 3-amino-1-hydroxypropylidene-1,1-bisphosphonic acid (pamidronate).

[2-(2-pyridinyl)ethylidene]-1,1-bisphosphonic acid (piridronate) is described in U.S. Patent No. 4,761,406, which is incorporated by reference in its entirety.

- 35 1-hydroxy-2-(3-pyridinyl)-ethylidene-1,1-bisphosphonic acid (risedronate).



(4-chlorophenyl)thiomethane-1,1-disphosphonic acid (tiludronate) as described in U.S. Patent 4,876,248, to Brelriere et al., October 24, 1989, which is incorporated by reference herein in its entirety.

5 1-hydroxy-2-(1H-imidazol-1-yl)ethylidene-1,1-bisphosphonic acid (zolendronate).

Preferred are bisphosphonates selected from the group consisting of alendronate, cimadronate, clodronate, tiludronate, etidronate, ibandronate, risedronate, piridronate, pamidronate,  
10 zolendronate, pharmaceutically acceptable salts thereof, and mixtures thereof.

More preferred is alendronate, pharmaceutically acceptable salts thereof, and mixtures thereof.

Most preferred is alendronate monosodium trihydrate.

#### 15 Pharmaceutical Compositions

Compositions useful in the present invention comprise a pharmaceutically effective amount of a bisphosphonate. The bisphosphonate is typically administered in admixture with suitable  
20 pharmaceutical diluents, excipients, or carriers, collectively referred to herein as "carrier materials", suitably selected with respect to oral administration, i.e. tablets, capsules, elixirs, syrups, effervescent compositions, powders, and the like, and consistent with conventional pharmaceutical practices. For example, for oral administration in the  
25 form of a tablet, capsule, or powder, the active ingredient can be combined with an oral, non-toxic, pharmaceutically acceptable inert carrier such as lactose, starch, sucrose, glucose, methyl cellulose, magnesium stearate, mannitol, sorbitol, croscarmellose sodium and the like; for oral administration in liquid form, e.g., elixirs and syrups,  
30 effervescent compositions, the oral drug components can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents, buffers, coatings, and coloring agents can also be incorporated. Suitable binders  
35 can include starch, gelatin, natural sugars such as a glucose, anhydrous

lactose, free-flow lactose, beta-lactose, and corn sweeteners, natural and synthetic gums, such as acacia, guar, tragacanth or sodium alginate, carboxymethyl cellulose, polyethylene glycol, waxes, and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. A particularly preferred tablet formulation for alendronate monosodium trihydrate is that described in U.S. Patent No. 5,358,941, to Bechard et al, issued October 25, 1994, which is incorporated by reference herein in its entirety. The compounds used in the present method can also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxylpropyl-methacrylamide, and the like.

The precise dosage of the bisphosphate will vary with the dosing schedule, the oral potency of the particular bisphosphonate chosen, the age, size, sex and condition of the mammal or human, the nature and severity of the disorder to be treated, and other relevant medical and physical factors. Thus, a precise pharmaceutically effective amount cannot be specified in advance and can be readily determined by the caregiver or clinician. Appropriate amounts can be determined by routine experimentation from animal models and human clinical studies. Generally, an appropriate amount of bisphosphonate is chosen to obtain a bone resorption inhibiting effect, i.e. a bone resorption inhibiting amount of the bisphosphonate is administered. For humans, an effective oral dose of bisphosphonate is typically from about 1.5 to about 6000 µg/kg body weight and preferably about 10 to about 2000 µg/kg of body weight.

For human oral compositions comprising alendronate, pharmaceutically acceptable salts thereof, or pharmaceutically acceptable derivatives thereof, a unit dosage typically comprises from about 8.75 mg to about 140 mg of the alendronate compound, on an alendronic acid active weight basis.

For once-weekly dosing, an oral unit dosage comprises from about 17.5 mg to about 70 mg of the alendronate compound, on an alendronic acid active weight basis. Examples of weekly oral dosages

include a unit dosage which is useful for osteoporosis prevention comprising about 35 mg of the alendronate compound, and a unit dosage which is useful for treating osteoporosis comprising about 70 mg of the alendronate compound.

- 5 For twice-weekly dosing, an oral unit dosage comprises from about 8.75 mg to about 35 mg of the alendronate compound, on an alendronic acid active weight basis. Examples of twice-weekly oral dosages include a unit dosage which is useful for osteoporosis prevention comprising about 17.5 mg of the alendronate compound, and  
10 a unit dosage which is useful for osteoporosis treatment, comprising about 35 mg of the alendronate compound.

- For biweekly or twice-monthly dosing, an oral unit dosage comprises from about 35 mg to about 140 mg of the alendronate compound, on an alendronic acid active weight basis. Examples of  
15 biweekly or twice-monthly oral dosages include a unit dosage which is useful for osteoporosis prevention comprising about 70 mg of the alendronate compound, and a unit dosage which is useful for osteoporosis treatment, comprising about 140 mg of the alendronate compound.

- 20 Nonlimiting examples of oral compositions comprising alendronate, as well as other bisphosphonates, are illustrated in the Examples, below.

25 Sequential Administration Of Histamine H2 Receptor Blockers And/Or Proton Pump Inhibitors With Bisphosphonates

- In further embodiments, the methods and compositions of the present invention can also comprise a histamine H2 receptor blocker (i.e. antagonist) and/or a proton pump inhibitor. Histamine H2 receptor blockers and proton pump inhibitors are well known therapeutic agents  
30 for increasing gastric pH. See L.J. Hixson, et al., *Current Trends in the Pharmacotherapy for Peptic Ulcer Disease*, Arch. Intern. Med., vol. 152, pp. 726-732 (April 1992), which is incorporated by reference herein in its entirety. It is found in the present invention that the sequential oral administration of a histamine H2 receptor blocker and/or a proton pump  
35 inhibitor, followed by a bisphosphonate can help to further minimize

adverse gastrointestinal effects. In these embodiments, the histamine H2 receptor blocker and/or proton pump inhibitor is administered from about 30 minutes to about 24 hours prior to the administration of the bisphosphonate. In more preferred embodiments, the histamine H2  
5 receptor blocker and/or proton pump inhibitor is administered from about 30 minutes to about 12 hours prior to the administration of the bisphosphate.

The dosage of the histamine H2 receptor blocker and/or proton pump inhibitor will depend upon the particular compound  
10 selected and factors associated with the mammal to be treated, i.e. size, health, etc.

Nonlimiting examples of histamine H2 receptor blockers and/or proton pump inhibitors include those selected from the group consisting of cimetidine, famotidine, nizatidine, ranitidine, omeprazole, and lansoprazole.  
15

#### Treatment Kits

In further embodiments, the present invention relates to a kit for conveniently and effectively carrying out the methods in  
20 accordance with the present invention. Such kits are especially suited for the delivery of solid oral forms such as tablets or capsules. Such a kit preferably includes a number of unit dosages. Such kits can include a card having the dosages oriented in the order of their intended use. An example of such a kit is a "blister pack". Blister packs are well known in  
25 the packaging industry and are widely used for packaging pharmaceutical unit dosage forms. If desired, a memory aid can be provided, for example in the form of numbers, letters, or other markings or with a calendar insert, designating the days in the treatment schedule in which the dosages can be administered. Alternatively,  
30 placebo dosages, or calcium or dietary supplements, either in a form similar to or distinct from the bisphosphonate dosages, can be included to provide a kit in which a dosage is taken every day. In those embodiments including a histamine H2 receptor and/or proton pump inhibitor, these agents can be included as part of the kit.

35

### EXAMPLES

5 The following examples further describe and demonstrate embodiments within the scope of the present invention. The examples are given solely for the purpose of illustration and are not to be construed as limitations of the present invention as many variations thereof are possible without departing from the spirit and scope of the invention.

#### EXAMPLE 1

##### 10 Esophageal Irritation Potential

The esophageal irritation potential of the bisphosphonates is evaluated using a dog model.

15 The experiments demonstrate the relative irritation potential of the following dosing regimens: placebo (Group 1), a single high concentration dosage of alendronate monosodium trihydrate (Group 2), a low concentration dosage of alendronate monosodium trihydrate administered for five consecutive days (Groups 3 and 4), a high concentration dosage of alendronate monosodium trihydrate administered once per week for four weeks (Group 5), a mid-range concentration dosage of alendronate monosodium trihydrate administered twice per week for four weeks (Group 6), a low dosage of risedronate sodium administered for five consecutive days (Group 7), and a low dosage of tiludronate disodium administered for five consecutive days (Group 8).

The following solutions are prepared:

- 25 (1) simulated gastric juice (pH about 2), i.e. the control solution.
- (2) simulated gastric juice (pH about 2) containing about 0.20 mg/mL of alendronate monosodium trihydrate on an alendronic acid active basis.
- 30 (3) simulated gastric juice (pH about 2) containing about 0.80 mg/mL of alendronate monosodium trihydrate on an alendronic acid active basis.

- (4) simulated gastric juice (pH about 2) containing about 0.40 mg/mL of alendronate monosodium trihydrate on an alendronic acid active basis.
- (5) simulated gastric juice (pH about 2) containing about 0.20 mg/mL of risedronate sodium on a risedronic acid active basis.
- (6) simulated gastric juice (pH about 2) containing about 4.0 mg/mL of tiludronate disodium on a tiludronic acid active basis.

15 The simulated gastric juice is prepared by dissolving about 960 mg of pepsin (L-585,228000B003, Fisher Chemical) in about 147 mL of 0.90 (wt %) NaCl (aqueous), adding about 3mL of 1.0 M HCl (aqueous), and adjusting the volume to about 300 mL with deionized water. The pH of the resulting solution is measured and if necessary is adjusted to about 2 using 1.0 M HCl (aqueous) or 1.0 M NaOH (aqueous).

20 The animals used in the experiments are anesthetized and administered about 50 mL of the appropriate solution over about 30 minutes by infusion into the esophagus using an infusion pump and a rubber catheter. The following treatment experiments are run:

25 Group 1: This control group contains four animals. Each animal is administered a dosage of about 50 mL of simulated gastric juice [solution (1)] on each of five consecutive days. The animals are sacrificed immediately after the last dose is administered.

30 Group 2: This group contains four animals. Each animal is administered a dosage of about 50 mL of simulated gastric juice containing about 0.20 mg/mL of alendronate [solution (2)] on each of five consecutive days. The animals are sacrificed immediately after the last dose is administered.

35 Group 3: This group contains five animals. Each animal is administered a dosage of about 50 mL of simulated gastric juice containing about 0.80 mg/mL of alendronate [solution (3)] on a

single treatment day. The animals are sacrificed about 24 hours after the dose is administered.

5 Group 4: This group contains five animals. Each animal is administered a dosage of about 50 mL of simulated gastric juice containing about 0.80 mg/mL of alendronate [solution (3)] on a single treatment day. The animals are sacrificed about 7 days after the dose is administered.

10 Group 5: This group contains six animals. Each animal is administered a dosage of about 50 mL of simulated gastric juice containing about 0.80 mg/mL of alendronate [solution (3)] once per week, i.e. every seven days, for four weeks. The animals are administered a total of four dosages. The animals are sacrificed about 7 days after the last dose is administered.

15 Group 6: This group contains six animals. Each animal is administered a dosage of about 50 mL of simulated gastric juice containing about 0.40 mg/mL of alendronate [solution (4)] twice per week, i.e. every three to four days, for four weeks. The animals are administered a total of eight dosages. The animals are sacrificed about four days after the last dose is administered.

20 Group 7: This group contains eight animals. Each animal is administered a dosage of about 50 mL of simulated gastric juice containing about 0.20 mg/mL of risedronate [solution (5)] on each of five consecutive days. The animals are sacrificed immediately after the last dose is administered.

25 Group 8: This group contains four animals. Each animal is administered a dosage of about 50 mL of simulated gastric juice containing about 4.0 mg/mL of tiludronate [solution (6)] on each of five consecutive days. The animals are sacrificed immediately after the last dose is administered.

30  
35

The esophagus from each sacrificed animal is removed and prepared for histopathology using standard techniques by embedding the tissue in paraffin, staining with hematoxylin and eosin. The sections are examined microscopically. The histopathology results are summarized in Table 1.

For the Group 1 animals (control group), the photomicrographs show that the esophagus is normal with an intact epithelium and absence of inflammatory cells in the submucosa. FIG. 1 is a representative photomicrograph from a Group 1 animal.

For the Group 2 animals, the photomicrographs show that the esophagus exhibits deep ulceration of the epithelial surface and marked submucosal inflammation and vacuolation. FIG. 2 is a representative photomicrograph from a Group 2 animal.

For the Group 3 animals, the photomicrographs show that the esophagus has an intact epithelial surface with very slight submucosal inflammation and vacuolation. FIG. 3 is a representative photomicrograph from a Group 3 animal.

For the Group 4 animals, the photomicrographs show that the esophagus has an intact epithelium with either minimal inflammation (two of the five animals) or no inflammation (three of the five animals) and no vacuolation. FIG. 4 is a representative photomicrograph from a Group 4 animal exhibiting minimal inflammation.

For the Group 5 animals, the photomicrographs show that the esophagus is normal with an intact epithelium and absence of inflammatory cells in the submucosa. FIG. 5 is a representative photomicrograph from a Group 5 animal.

For the Group 6 animals, the photomicrographs show that the esophagus exhibits deep ulceration of the epithelial surface and marked submucosal inflammation and vacuolation. FIG. 6 is a representative photomicrograph from a Group 6 animal.

For the Group 7 animals, the photomicrographs show that the esophagus exhibits deep ulceration of the epithelial surface and marked submucosal inflammation and vacuolation. FIG. 7 is a representative photomicrograph from a Group 7 animal.



For the Group 8 animals, the photomicrographs show that the esophagus exhibits slight ulceration of the epithelial surface and slight submucosal inflammation and vacuolation. FIG. 8 is a representative photomicrograph from a Group 8 animal.

5

These experiments demonstrate that considerably less esophageal irritation (comparable to control Group 1) is observed from the administration of a single high concentration dosage of alendronate (Groups 3 and 4) versus administration of low concentration dosages on consecutive days (Group 2). These experiments also demonstrate considerably less esophageal irritation is observed from the administration of a single high concentration of alendronate on a weekly basis (Group 5) or twice-weekly basis (Group 6) versus administration of low concentration dosages on consecutive days (Group 2). These experiments also demonstrate that when other bisphosphonates such as risedronate (Group 7) or tiludronate (Group 8) are administered at low dosages on consecutive days that the esophageal irritation potential is high.

10

15

Table 1.

Esophageal Irritation Potential Studies				
Group	Active Agent mg/mL	Dosing Schedule	Sacrifice Time	Histo-pathology
1 (n=4)	0	1X daily for 5 days	immediate ly after last dosing	Normal. Intact epithelium and absence of inflammatory cells in the submucosa.
2 (n=4)	Alendronate 0.20	1X daily for 5 days	immediate ly after last dosing	Deep ulceration of epithelial surface. Marked submucosal inflammation and vacuolation.
3 (n=5)	Alendronate 0.80	1X	24 hours after dosing	Intact epithelial surface with very slight submucosal inflammation and vacuolation.
4 (n=5)	Alendronate 0.80	1X	7 days after dosing	Intact epithelium with either minimal inflammation (2 of 5 animals) or no inflammation (3 of 5 animals) and no vacuolation.
5 (n=6)	Alendronate 0.80	1X weekly for a total of 4 doses	7 days after last dosing	Intact epithelium with no inflammation and no vacuolation.

6 (n=6)	Alendronate 0.40	2X weekly for 4 weeks	immediate ly after last dosing	Deep ulceration of epithelial surface. Marked submucosal inflammation and vacuolation.
7 (n=8)	Risedronate 0.20	1X daily for 5 days	immediate ly after last dosing	Deep ulceration of epithelial surface (4 of 8 animals). Marked submucosal inflammation and vacuolation.
8 (n=4)	Tiludronate 4.0	1X daily for 5 days	24 hours after last dosing	Slight submucosal inflammation and vacuolation (3 of 4 animals, including 1 of these animals with slight ulceration).

### EXAMPLE 2

Once-weekly dosing regimen.

5

Treatment of osteoporosis.

Alendronate tablets or liquid formulations containing about 70 mg of alendronate, on an alendronic acid active basis, are prepared (see EXAMPLES 7 and 8). The tablets or liquid formulations are orally administered to a human patient once-weekly, i.e. preferably about once every seven days (for example, every Sunday), for a period of at least one year. This method of administration is useful and convenient for treating osteoporosis and for minimizing adverse gastrointestinal effects, particularly adverse esophageal effects. This method is also useful for improving patient acceptance and compliance.

15

Prevention of osteoporosis.

Alendronate tablets or liquid formulations containing about 35 mg of alendronate, on an alendronic acid active basis, are prepared (see EXAMPLES 7 and 8). The tablets or liquid formulations are orally administered to a human patient once-weekly, i.e. preferably about once every seven days (for example, every Sunday), for a period of at least one year. This method of administration is useful and convenient for preventing osteoporosis and for minimizing adverse gastrointestinal effects, particularly adverse esophageal effects. This method is also useful for improving patient acceptance and compliance.

### EXAMPLE 3

Twice-weekly dosing regimen.

Treatment of osteoporosis.

Alendronate tablets or liquid formulations containing about 35 mg of alendronate, on an alendronic acid active basis, are prepared (see EXAMPLES 7 and 8). The tablets or liquid formulations are orally administered to a human patient twice-weekly, preferably about once every three or four days (for example, every Sunday and Wednesday), for a period of at least one year. This method of administration is useful and convenient for treating osteoporosis and for minimizing adverse gastrointestinal effects, particularly adverse esophageal effects. This method is also useful for improving patient acceptance and compliance.

Prevention of osteoporosis.

Alendronate tablets or liquid formulations containing about 17.5 mg of alendronate, on an alendronic acid active basis, are prepared (see EXAMPLES 7 and 8). The tablets or liquid formulations are orally administered to a human patient twice-weekly, preferably about once every three or four days (for example, every Sunday and Wednesday), for a period of at least one year. This method of administration is useful and convenient for preventing osteoporosis and for minimizing adverse

gastrointestinal effects, particularly adverse esophageal effects. This method is also useful for improving patient acceptance and compliance.

#### EXAMPLE 4

5

Biweekly dosing regimen

Treatment of osteoporosis.

- Alendronate tablets or liquid formulations containing about
- 10 140 mg of alendronate, on an alendronic acid active basis, are prepared (see EXAMPLES 7 and 8). The tablets or liquid formulations are orally administered to a human patient biweekly, i.e. preferably about once every fourteen days (for example, on alternate Sundays), for a period of at least one year. This method of administration is useful and
- 15 convenient for treating osteoporosis and for minimizing adverse gastrointestinal effects, particularly adverse esophageal effects. This method is also useful for improving patient acceptance and compliance.

Prevention of osteoporosis.

- 20 Alendronate tablets or liquid formulations containing about 70 mg of alendronate, on an alendronic acid active basis, are prepared (see EXAMPLES 7 and 8). The tablets or liquid formulations are orally administered to a human patient biweekly, i.e. preferably about once every fourteen days (for example, on alternate Sundays), for a period of
- 25 at least one year. This method of administration is useful and convenient for preventing osteoporosis and for minimizing adverse gastrointestinal effects, particularly adverse esophageal effects. This method is also useful for improving patient acceptance and compliance.

30

#### EXAMPLE 5

Twice-monthly dosing regimen.

Treatment of osteoporosis.

Alendronate tablets or liquid formulations containing about 140 mg of alendronate, on an alendronic acid active basis, are prepared (see EXAMPLES 7 and 8). The tablets or liquid formulations are orally administered to a human twice-monthly, i.e. preferably about once every fourteen to sixteen days (for example, on about the first and fifteenth of each month), for a period of at least one year. This method of administration is useful and convenient for treating osteoporosis and for minimizing adverse gastrointestinal effects, particularly adverse esophageal effects. This method is also useful for improving patient acceptance and compliance.

#### Prevention of osteoporosis.

Alendronate tablets or liquid formulations containing about 70 mg of alendronate, on an alendronic acid active basis, are prepared (see EXAMPLES 7 and 8). The tablets or liquid formulations are orally administered to a human patient biweekly, i.e. preferably once every fourteen to sixteen days (for example, on about the first and fifteenth of each month), for a period of at least one year. This method of administration is useful and convenient for preventing osteoporosis and for minimizing adverse gastrointestinal effects, particularly adverse esophageal effects. This method is also useful for improving patient acceptance and compliance.

#### EXAMPLE 6

In further embodiments, alendronate tablets or liquid formulations are orally dosed, at the desired dosage, according to the dosing schedules of EXAMPLES 2-5, for treating or preventing other disorders associated with abnormal bone resorption.

In yet further embodiments, other bisphosphonate compounds are orally dosed, at the desired dosage, according to the dosing schedules of EXAMPLES 2-5, for treating or preventing osteoporosis or for treating or preventing other conditions associated with abnormal bone resorption.

EXAMPLE 7

Bisphosphonate tablets.

- 5           Bisphosphonate containing tablets are prepared using standard mixing and formation techniques as described in U.S. Patent No. 5,358,941, to Bechard et al., issued October 25, 1994, which is incorporated by reference herein in its entirety.

- 10           Tablets containing about 35 mg of alendronate, on an alendronic acid active basis, are prepared using the following relative weights of ingredients.

	<u>Ingredient</u>	<u>Per Tablet</u>	<u>Per 4000 Tablets</u>
15	Alendronate Monosodium Trihydrate	45.68 mg	182.72 g
	Anhydrous Lactose, NF	71.32 mg	285.28 g
	Microcrystalline Cellulose, NF	80.0 mg	320.0 g
20	Magnesium Stearate, NF	1.0 mg	4.0 g
	Croscarmellose Sodium, NF	2.0 mg	8.0 g

- 25           The resulting tablets are useful for administration in accordance with the methods of the present invention for inhibiting bone resorption.

- 30           Similarly, tablets comprising other relative weights of alendronate, on an alendronic acid active basis are prepared: e.g., about 8.75, 17.5, 70, and 140 mg per tablet. Also, tablets containing other bisphosphonates at appropriate active levels are similarly prepared: e.g., cimidronate, clodronate, tiludronate, etidronate, ibandronate, risedronate, piridronate, pamidronate, zolendronate, and pharmaceutically acceptable salts thereof. Also, tablets containing
- 35           combinations of bisphosphonates are similarly prepared.

EXAMPLE 8

## Liquid Bisphosphonate Formulation.

5

Liquid bisphosphonate formulations are prepared using standard mixing techniques.

A liquid formulation containing about 70 mg of alendronate monosodium trihydrate, on an alendronic acid active basis, per about 75 mL of liquid is prepared using the following relative weights of ingredients.

	<u>Ingredient</u>	<u>Weight</u>
15	Alendronate Monosodium Trihydrate	91.35 mg
	Sodium Propylparaben	22.5 mg
	Sodium Butylparaben	7.5 mg
	Sodium Citrate Dihydrate	1500 mg
20	Citric Acid Anhydrous	56.25 mg
	Sodium Saccharin	7.5 mg
	Water	qs 75 mL
	1 N Sodium Hydroxide (aq)	qs pH 6.75

25 The resulting liquid formulation is useful for administration as a unit dosage in accordance with the methods of the present invention for inhibiting bone resorption.

Similarly, liquid formulations comprising other relative weights of alendronate, on an alendronic acid active basis, per unit dosage are prepared: e.g., about 8.75, 17.5, 35, and 140 mg per 75 mL volume. Also, the liquid formulations are prepared to provide other volumes for the unit dosage, e.g. about 135 mL. Also, the liquid formulations are prepared containing other bisphosphonates at appropriate active levels: e.g., cimidronate, clodronate, tiludronate, 35 etidronate, ibandronate, risedronate, piridronate, pamidronate,



zolendronate, and pharmaceutically acceptable salts thereof. Also, liquid formulations containing combinations of bisphosphonates are similarly prepared.

09445837-121399

WHAT IS CLAIMED IS:

1. A method for inhibiting bone resorption in a mammal, said method comprising orally administering to said mammal a pharmaceutically effective amount of a bisphosphonate as a unit dosage according to a continuous schedule having a dosing interval selected from the group consisting of once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing.
2. A method according to Claim 1 wherein said bisphosphonate is selected from the group consisting of alendronate, cimadronate, clodronate, tiludronate, etidronate, ibandronate, risedronate, piridronate, pamidronate, zolendronate, pharmaceutically acceptable salts thereof, and mixtures thereof.
3. A method according to Claim 1 wherein said bisphosphonate is selected from the group consisting of alendronate, pharmaceutically acceptable salts thereof, and mixtures thereof.
4. A method according to Claim 3 wherein said pharmaceutically acceptable salt is alendronate monosodium trihydrate.
5. A method according to Claim 4 wherein said mammal is a human.
6. A method for treating osteoporosis in a mammal in need of such treatment, said method comprising orally administering to said mammal a pharmaceutically effective amount of a bisphosphonate as a unit dosage according to a continuous schedule having a dosing interval selected from the group consisting of once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing.
7. A method according to Claim 6 wherein said mammal is a human.

8. A method according to Claim 7 wherein said dosing interval is once-weekly and said unit dosage comprises about 70 mg of alendronate monosodium trihydrate, on an alendronic acid active basis.

9. A method according to Claim 7 wherein said dosing interval is twice-weekly and said unit dosage comprises about 35 mg of alendronate monosodium trihydrate, on an alendronic acid active basis

10. A method according to Claim 7 wherein said dosing interval is biweekly and said unit dosage comprises about 140 mg of alendronate monosodium trihydrate, on an alendronic acid active basis.

11. A method according to Claim 7 wherein said dosing interval is twice-monthly and said unit dosage comprises about 140 mg of alendronate monosodium trihydrate, on an alendronic acid active basis.

12. A method for preventing osteoporosis in a mammal in need of such treatment, said method comprising orally administering to said mammal a pharmaceutically effective amount of a bisphosphonate as a unit dosage according to a continuous schedule having a dosing interval selected from the group consisting of once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing.

13. A method according to Claim 12 wherein said mammal is a human.

14. A method according to Claim 13 wherein said dosing interval is once-weekly and said unit dosage comprises about 35 mg of alendronate monosodium trihydrate, on an alendronic acid active basis.

15. A method according to Claim 13 wherein said dosing interval is twice-weekly and said unit dosage comprises about 17.5 mg of alendronate monosodium trihydrate, on an alendronic acid active basis.

16. A method according to Claim 13 wherein said dosing interval is biweekly and said unit dosage comprises about 70 mg of alendronate monosodium trihydrate, on an alendronic acid active basis.

17. A method according to Claim 13 wherein said dosing interval is twice-monthly and said unit dosage comprises about 70 mg of alendronate monosodium trihydrate, on alendronic acid active basis.

18. A method for inhibiting bone resorption in a mammal, said method comprising orally administering to said mammal a pharmaceutically effective amount of a bisphosphonate as a unit dosage according to a continuous schedule having a periodicity from about once every 3 days to about once every 16 days.

19. A method for treating osteoporosis in a mammal, said method comprising orally administering to said mammal a pharmaceutically effective amount of a bisphosphonate as a unit dosage according to a continuous schedule having a periodicity from about once every 3 days to about once every 16 days.

20. A method for preventing osteoporosis in a mammal, said method comprising orally administering to said mammal a pharmaceutically effective amount of a bisphosphonate as a unit dosage according to a continuous schedule having a periodicity from about once every 3 days to about once every 16 days.

21. A method according to any of Claims 1 - 20 wherein said unit dosage of said bisphosphonate comprises from about 1.5 to about 6000  $\mu\text{g/kg}$  body weight.

22. A method according to any of Claims 1 - 20 wherein said unit dosage of said bisphosphonate comprises from about 10 to about 2000  $\mu\text{g/kg}$  body weight.

23. A method for inhibiting bone resorption in a mammal comprising sequentially orally administering to said mammal a pharmaceutically effective amount of a unit dosage of a histamine H<sub>2</sub> receptor blocker or a proton pump inhibitor and a unit dosage of a bisphosphonate according to a continuous schedule having a periodicity from about once every 3 days to about once every 16 days.

24. A method for inhibiting bone resorption in a mammal comprising sequentially orally administering to said human a pharmaceutically effective amount of a unit dosage of a histamine H2 receptor blocker or a proton pump inhibitor and a unit dosage of a bisphosphonate according to a continuous schedule having a dosing interval selected from the group consisting of once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing.

25. A method according to Claim 24 wherein said histamine H2 receptor blocker or said proton pump inhibitor is administered from about 30 minutes to about 24 hours prior to the administration of said bisphosphonate.

26. A method according to Claim 24 wherein said bisphosphonate is selected from the group consisting of alendronate, cimadronate, clodronate, tiludronate, etidronate, ibandronate, risedronate, pirdronate, pamidronate, zoledronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof.

27. A method according to any of Claims 23-26 wherein said histamine H2 receptor blocker or proton pump inhibitor is selected from the group consisting of cimetidine, famotidine, nizatidine, ranitidine, omeprazole, and lansoprazole.

28. A kit comprising, comprising:

- (a) at least one pharmaceutically effective unit oral dosage of a bisphosphonate for oral administration, and
- (b) at least one pharmaceutically effective unit dosage of a histamine H2 receptor blocker or a proton pump inhibitor.

29. A kit according to Claim 28 wherein said bisphosphonate is selected from the group consisting of alendronate, cimadronate, clodronate, tiludronate, etidronate, ibandronate, risedronate, pirdronate, pamidronate, zoledronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof.

30. A kit according to any of Claims 29 wherein said histamine H2 receptor blocker or proton pump inhibitor is selected from the group consisting of cimetidine, famotidine, nizatidine, ranitidine, omeprazole, and lansoprazole.

31. Use of a bisphosphonate for the manufacture of a medicament for inhibiting bone resorption in a mammal wherein said medicament is adapted for oral administration in a unit dosage form according to a continuous schedule having a periodicity from about once every 3 days to about once every 16 days.

32. Use of a bisphosphonate for the manufacture of a medicament for inhibiting bone resorption in a mammal wherein said medicament is adapted for oral administration in a unit dosage form according to a continuous schedule having a dosing interval selected from the group consisting of once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing.

33. Use of a bisphosphonate according to Claim 32 wherein said bisphosphonate is selected from the group consisting of alendronate, cimidronate, clodronate, tiludronate, etidronate, ibandronate, risedronate, piridronate, pamidronate, zoledronate, pharmaceutically acceptable salts thereof, and mixtures thereof

34. Use of a bisphosphonate according to Claim 32 wherein said bisphosphonate is selected from the group consisting of alendronate, pharmaceutically acceptable salts thereof, and mixtures thereof.

35. Use of a bisphosphonate according to Claim 34 wherein said pharmaceutically acceptable salt is alendronate monosodium trihydrate.

36. Use of a bisphosphonate according to Claim 35 wherein said mammal is a human.

0445837.121399

37. Use of a bisphosphonate for the manufacture of a medicament for treating osteoporosis in a mammal in need thereof wherein said medicament is adapted for oral administration in a unit dosage form according to a continuous schedule having a periodicity from about once every 3 days to about once every 16 days.

38. Use of a bisphosphonate for the manufacture of a medicament for treating osteoporosis in a mammal in need thereof wherein said medicament is adapted for oral administration in a unit dosage form according to a continuous schedule having a dosing interval selected from the group consisting of once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing.

39. Use of a bisphosphonate according to Claim 38 wherein said mammal is a human.

40. Use of a bisphosphonate according to Claim 39 wherein said dosing interval is once-weekly and said unit dosage comprises about 70 mg of alendronate monosodium trihydrate, on an alendronic acid active basis.

41. Use of a bisphosphonate according to Claim 39 wherein said dosing interval is twice-weekly and said unit dosage comprises about 35 mg of alendronate monosodium trihydrate, on an alendronic acid active basis.

42. Use of a bisphosphonate for the manufacture of a medicament for preventing osteoporosis in a mammal in need thereof wherein said medicament is adapted for oral administration in a unit dosage form according to a continuous schedule having a periodicity from about once every 3 days to about once every 16 days.

43. Use of a bisphosphonate for the manufacture of a medicament for preventing osteoporosis in a mammal in need thereof wherein said medicament is adapted for oral administration in a unit dosage form according to a continuous schedule having a dosing interval selected from the group consisting of once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing.

44. Use of a bisphosphonate according to Claim 43 wherein said mammal is a human.

45. Use of a bisphosphonate according to Claim 44 wherein said dosing interval is once-weekly and said unit dosage comprises about 35 mg of alendronate monosodium trihydrate, on an alendronic acid active basis.

46. Use of the combination of a bisphosphonate and a histamine H2 receptor blocker or a proton pump inhibitor for the manufacture of a medicament for inhibiting bone resorption in a mammal comprising sequentially orally administering to said mammal a pharmaceutically effective amount of a unit dosage of a histamine H2 receptor blocker or a proton pump inhibitor and a unit dosage of a bisphosphonate according to a continuous schedule having a periodicity from about once every 3 days to about once every 16 days

47. Use of the combination of a bisphosphonate and a histamine H2 receptor blocker or a proton pump inhibitor for the manufacture of a medicament for inhibiting bone resorption in a mammal comprising sequentially orally administering to said mammal a pharmaceutically effective amount of a unit dosage of a histamine H2 receptor blocker or a proton pump inhibitor and a unit dosage of a bisphosphonate according to a continuous schedule having a dosing interval selected from the group consisting of once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing.

48. A pharmaceutical kit useful for inhibiting bone resorption in a mammal comprising at least one pharmaceutically effective unit dosage of a bisphosphonate for oral administration according to a continuous schedule characterized in that

- (a) said unit dosage of said bisphosphonate comprises about 70 mg, on an alendronic acid active basis, of a bisphosphonate selected from the group consisting of alendronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof.
- (b) said continuous schedule is once-weekly, and
- (c) said kit comprises a memory aid for administering said unit dosages.

09445837.1/2139



49. A pharmaceutical kit according to claim 48 wherein said unit dosages are oriented in said pharmaceutical kit in the order of their intended use

50. A pharmaceutical kit according to claim 49 wherein said memory aid indicates that said unit dosage is administered once a week.

51. A pharmaceutical kit according to claim 50 wherein said memory aid indicates a unit dosage is administered on each of week 1, week 2, week 3, and week 4

52. A pharmaceutical kit according to claim 51 wherein said memory aid indicates that said unit dosage is administered once during a seven day period

0445837.121399

~~41~~  
43

Substitute Sheet

AMENDED SHEET

TOTAL P.005

TITLE OF THE INVENTION  
METHOD FOR INHIBITING BONE RESORPTION

ABSTRACT OF THE INVENTION

- 5           Disclosed are methods for inhibiting bone resorption in mammals while minimizing the occurrence of or potential for adverse gastrointestinal effects. Also disclosed are pharmaceutical compositions and kits for carrying out the therapeutic methods disclosed herein. The compounds are bisphosphonates selected from the group consisting of alendronate,
- 10   cimadronate, clodronate, tiludronate, etidronate, ibandronate, risedronate, piridronate, pamidronate, zoledronate, optionally in combination with a histamine H2 antagonist.

09445837.1 121399  
66E27 2E84H6

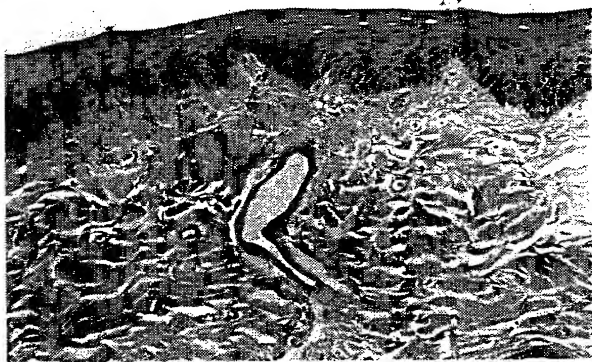


FIG. 1

2/8

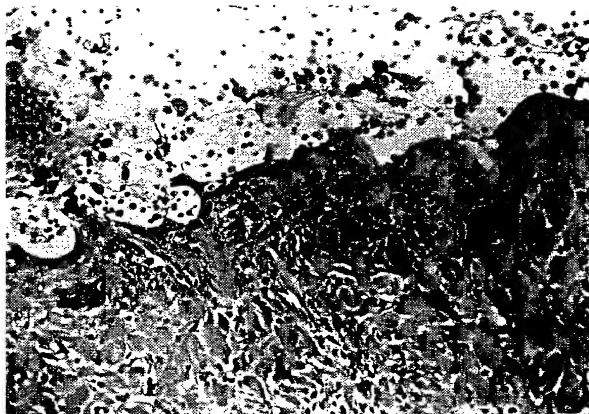


FIG.2

3/8

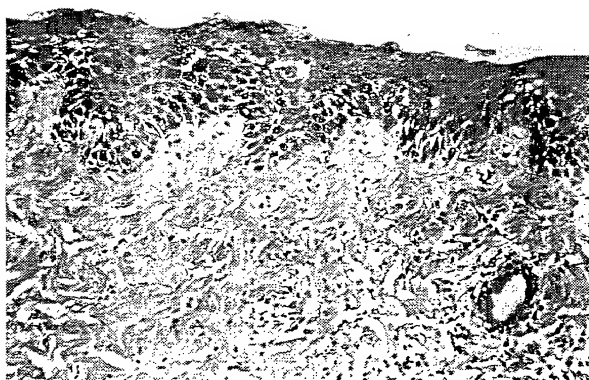


FIG.3

4/8

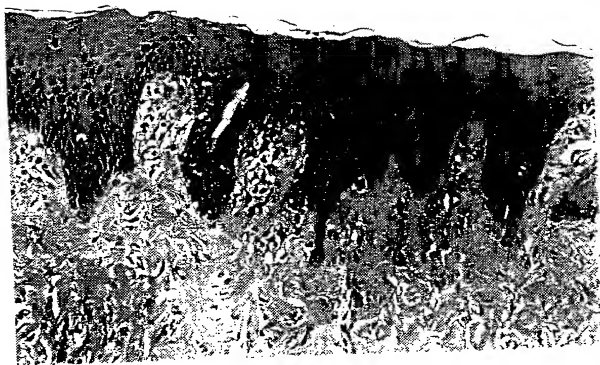


FIG.4

5/8

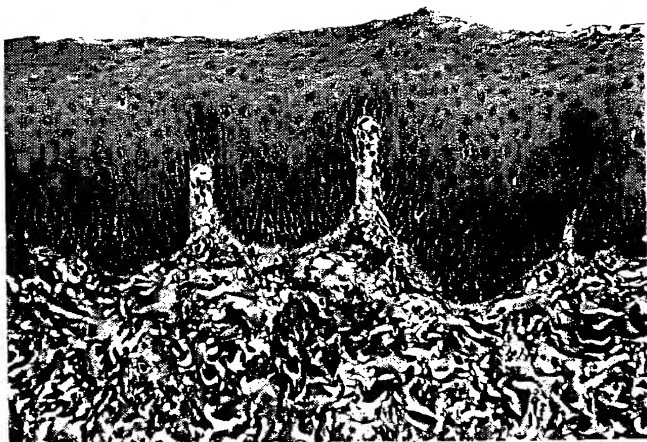


FIG.5

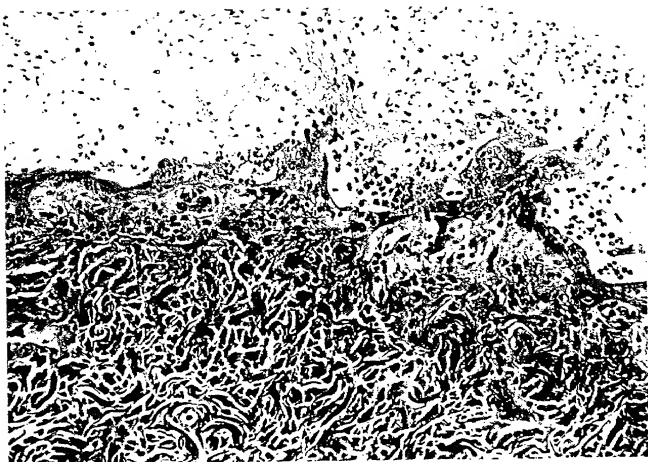


FIG.6



7/8



FIG.7



FIG. 8

**COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY**  
(Includes Reference to PCT International Applications)

ATTORNEY'S DOCKET NUMBER  
20002YP

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

**METHOD FOR INHIBITING BONE RESORPTION**

the specification of which (check only one item below):

☐ is attached hereto.

☐ was filed as United States application

Serial No \_\_\_\_\_

on \_\_\_\_\_

and was amended

on \_\_\_\_\_ (if applicable).

☒ was filed as PCT international application

Number PCT/US98/14796

on 17-Jul-1998

and was amended under PCT Article 19

on \_\_\_\_\_ (if applicable).

☐ is being filed as PCT international application, Attorney Docket No. \_\_\_\_\_

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the patentability of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate or of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed:

**PRIOR FOREIGN/PCT APPLICATION(S) AND ANY PRIORITY CLAIMS UNDER 35 U.S.C. 119:**

COUNTRY (if PCT, indicate "PCT")	APPLICATION NUMBER	DATE OF FILING (day, month, year)	PRIORITY CLAIMED UNDER 35 USC 119
GREAT BRITAIN	9717850.3	22-Aug-1997	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
GREAT BRITAIN	9717590.5	20-Aug-1997	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
			<input type="checkbox"/> YES <input type="checkbox"/> NO
			<input type="checkbox"/> YES <input type="checkbox"/> NO
			<input type="checkbox"/> YES <input type="checkbox"/> NO

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) or PCT international application(s) designating the United States of America that is/are listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in that/those prior application(s) in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application(s) and the national or PCT international filing date of this application:

**PRIOR U.S. APPLICATIONS OR PCT INTERNATIONAL APPLICATIONS DESIGNATING THE U.S. FOR BENEFIT UNDER 35 U.S.C. 120:**

U.S. APPLICATIONS		STATUS (Check one)		
U.S. APPLICATION NUMBER	U.S. FILING DATE	PATENTED	PENDING	ABANDONED
60/053,535	23-Jul-1997			x
60/053,351	22-Jul-1997			x

**PCT APPLICATIONS DESIGNATING THE U.S.**

PCT APPLICATION NO.	PCT FILING DATE	U.S. SERIAL NUMBERS ASSIGNED (if any)	PATENTED	PENDING	ABANDONED

**POWER OF ATTORNEY:** As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith. (List name and registration number)

ANTHONY D. SABATELLI Reg. No. 34,714	MELVIN WINOKUR Reg. No. 32,763	JOSEPH F. DIPRIMA Reg. No. 28,944
---	-----------------------------------	--------------------------------------

**Send Correspondence to:**

ANTHONY D. SABATELLI  
 Merck & Co., Inc.  
 P.O. Box 2000, 126 East Lincoln Avenue  
 Rahway, New Jersey 07065

**Direct Telephone Calls to:**  
 (name and telephone number)  
 (732)594-1935

	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME
202	RESIDENCE & CITIZENSHIP	CITY WESTFIELD	STATE OR FOREIGN COUNTRY NEW JERSEY	COUNTRY OF CITIZENSHIP U.S.A.
	POST OFFICE ADDRESS	POST OFFICE ADDRESS P.O. BOX 2000	CITY RAHWAY	STATE & ZIP CODE/COUNTRY NEW JERSEY 07065
203	RESIDENCE & CITIZENSHIP	CITY WATCHUNG	STATE OR FOREIGN COUNTRY NEW JERSEY	COUNTRY OF CITIZENSHIP U.S.A.
	POST OFFICE ADDRESS	POST OFFICE ADDRESS P.O. BOX 2000	CITY RAHWAY	STATE & ZIP CODE/COUNTRY NEW JERSEY 07065
203	RESIDENCE & CITIZENSHIP	CITY WESTFIELD	STATE OR FOREIGN COUNTRY NEW JERSEY	COUNTRY OF CITIZENSHIP U.S.A.
	POST OFFICE ADDRESS	POST OFFICE ADDRESS P.O. BOX 2000	CITY RAHWAY	STATE & ZIP CODE/COUNTRY NEW JERSEY 07065

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

SIGNATURE OF INVENTOR 201 	SIGNATURE OF INVENTOR 202 	SIGNATURE OF INVENTOR 203 
DATE 11/17/99	DATE 11/19/99	DATE 11/17/99